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A STUDY OF THE AXIS-CYLINDERS IN FIVE CASES OF GLIOMA CEREBRI

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It is not infrequently observed in a variety of neuropathological conditions, such as multiple sclerosis, tuberculoma, areas of compression and gliomata, that the necropsy reveals a much more extensive process than could have been even suspected from a most thorough clinical examination. This disproportion between the diseased area and the symptoms induced is, perhaps, more pronounced in gliomata than in any other condition, and it is to this pathological state that my attention has been directed.

It is well known that gliomata may exist for months or even years without causing either general or localizing symptoms of brain tumor. This might be conceivable where the tumor is situated in a silent area. According to Brush (1), however, such may be the case even though a localizing center be involved, and several cases have been reported in which no abnormal condition was manifested during life. On the other hand, those cases which do make themselves obvious to the clinician, occasionally show so few symptoms or else they have existed for so short a time that one is quite surprised when the pathologist presents him with a specimen in which one or more lobes, or a greater part of the brain stem is markedly involved; while a still more interesting feature is the occasional absence of degenerative changes above or below the lesion. Considering the ordinarily slow growth of such tumors, the questions naturally arise: How are we to explain this persistence of function and absence of degenerative changes where the cerebral tissue is extensively involved; and how are we to account for the apparently rapid cases which show a pathological state similar to those existing for months or even years?

The answer to the first question will naturally include the second, for if we can explain the persistence of function in simple uncomplicated gliomata, and if we admit that they can exist for years without producing symptoms; then the so-called rapid cases might easily be due to some intercurrent condition, such as hemorrhage, areas of softening or myxomatous changes in a pre-existing gliomatous mass which had hitherto been quiescent. However this may be, it shall be my effort to demonstrate that in simple cerebral gliomata persistence of function and absence of degenerative changes in the spinal cord may be explained upon a definite histological basis.

Let us review first the theories which have been offered in explanation of these facts.

From a study of the few cases which have been examined with this object in view, two rather theoretical explanations may be formulated. The first might be called the theory of displacement and is well illustrated in the case reported by Schorstein and Walton (2), who studied a glioma of the pons in a male child four years of age. Examination revealed slight spasticity of the lower extremities, more marked in the right side, and some weakness in the right arm. The left arm was practically normal. Increased knee jerks, no ankle clonus, and Babinski was negative. Duration—two months. There was found at autopsy a tumor measuring 2 x 1½ inches, situated in the left half of the pons and medulla, with slight invasion of the right half. The new growth passed gradually into the surrounding normal tissue, and showed in its center an area of softening. Microscopic sections were made from each half of the pons and from six different regions of the spinal cord. Those from the pons were stained with polychrome methylene blue. The right half showed some normal pontal tissue with many disarranged pyramidal fibers in the midst of a cellular tumor. The left half showed no normal pontal tissue, and an apparent absence of the transverse pontal and pyramidal fibers. Sections from the cord were stained with Busch's fluid, and hemalum and Van Gieson. Those stained by the former method showed no degenerative changes in any part, while the Van Gieson stain revealed the usual number of axis-cylinders.

Although the clinical findings and pathological condition at the site of the lesion were somewhat at variance, it is the absence of degenerative changes in the cord which constitutes the striking feature in this case. How could there be complete absence of pyramidal fibers in the left pontal region, with decided evidence of functional disturbance, and yet no sign of degeneration in the spinal cord? The author's explanation was that the left pyramidal fibers had been "pushed aside" without an interruption in continuity, although functionally inadequate. This seems to be a purely theoretical assumption, for it appears likely that had the fibers of the left side been displaced into the right pontal area, then this right half should have shown a definite increase in the number of pyramidal fasciculi, for it would have contained not only the fibers normally present, but those contributed from the left half. This should have been apparent to the naked eye on cut surface, yet no mention was made of such an observation. On the other hand, what has become of the transverse pontal fibers of the left half, which, it will be remembered, were entirely absent; and why were there no cerebellar symptoms pointing to their apparent destruction? Unfortunately no sections were made from the middle cerebellar peduncles and no evidence was adduced to account for the absence of the left pontal fibers. Furthermore, if this idea of displacement without anatomical interruption or other evidence of histological changes in the fibers be correct, why were the symptoms confined to the pyramidal system; none from the pontal fibers in the very heart of the tumor; and the whole symptom complex of only two months' duration? All of this may be due to pressure changes; yet why were there no pressure symptoms during the process of displacement, for surely the tumor did not attain such dimensions, push all the fasciculi to the right side and destroy the left pontal fibers in only two months.

In Davis' (3) case, for instance, there was found a glioma of the left frontal region, measuring 11 x 9 x 6 cm., which had pushed the thalamus, caudate nucleus and internal capsule to the right and posteriorly. The symptoms, which were "very slight," were of only two months' duration. Of course, this may be explained in two ways—one may say it was a very rapidly growing tumor or else it was a more gradual process which, after reaching certain dimensions, began to exert pressure changes, and that the first symptoms were evidences of this beginning pressure, which in two months attained such proportions as were found post-mortem. But evidently a tumor of the frontal region would have to attain considerable size before producing the displacement found in this case, and if size be any indication of chronicity, must have existed for some time. What, then, was the condition of affairs during the incipient stage? Surely there must have been some pressure exerted, and Marinesco and Minea (4) have shown that even very slight pressure of the shortest duration experimentally produced is sufficient to cause definite histological changes in the nervous system. Why, then, were the symptoms delayed until such marked displacement occurred? No report was made upon the spinal cord or the internal capsule.

Other cases might be reviewed in which there have been marked evidences of pressure changes, but they have been so incompletely studied from a pathological point of view that an abstract of them is scarcely worth while. In all the usual occurrence of a large tumor and relatively few symptoms were observed, but no report was made upon the condition of the nerve fibers involved by the new growth.

While it is not my intention to deny the occurrence of decided pressure symptoms and evidence of displacement in gliomata, it does not seem that such facts satisfactorily account for all the conditions observed. The objections, then, to such an explanation are: First, the failure to demonstrate that all the fasciculi are "pushed aside"; second, that it does not account for the absence of symptoms during the earlier stages when the infiltrating cells are in intimate contact with and no doubt exerting some pressure upon individual fibers; and lastly, it is thoroughly inadequate, in those cases where the entire pons or internal capsule shows no normal fasciculi upon macroscopic examination, nor any evidence of displacement.

The second and more widely accepted view rests upon the infiltrating nature of gliomata and the presence of medullated fibers in the tumor substance. Such observations led to the conclusion that the persistence of function and absence of degenerative changes below the lesion were due to these retained nerve fibers which passed through the tumor without interruption.

Sir William Gowers (5), in writing of gliomata, says: " Some infiltrate without displacing the cerebral substance, others displace rather than invade. From their infiltrating character they usually cause simple enlargement without displacement or compression of adjacent parts," and " sometimes nerve fibers persist and retain their conducting power in a part which is almost entirely infiltrated with the new growth." This seems to be the position taken by the majority of investigators who have demonstrated the presence of nerve fibers in gliomatous tissue. However, the conclusion that the fibers pass through without interruption does not appear to have been definitely proven, since most of the observations were made from small fragments of the tumor without any report upon the region above or below the new growth. Although one might find a few scattered fibers in a single portion of a tumor this is not sufficient to prove that they pass through as continuous neurones, for sections made from a greater depth in the same area or from the central portion of the tumor might show an entire absence of fibers, and no case was reported in which the entire neoplasm had been sectioned. Furthermore, it is a common observation that the usual medullary stains reveal a decreasing number of fibers from the periphery toward the center, while certain gliomatous areas show an entire absence of medullated fibers.

Bassoe's (6) monograph is interesting in this connection. In one of his three cases there was a large glioma of the left temporal and occipital lobes. The tumor was quite vascular and contained hemorrhagic areas with softening and necrosis. There was no mention of displacement of surrounding parts. The Walters-Kaes myelin stain showed numerous medullated fibers " passing through " the tumor. No degeneration was found in the spinal cord. Stain not mentioned; presumably the Walters-Kaes method was used. It is not quite clear as to what the author means, when he says numerous fibers were " passing through " the tumor. If he intends to convey the idea that they were passing through that portion of the tumor he examined, the point is quite admissible. On the other hand, if he takes the position that, since fibers were found in the tumor and no degeneration was observed in the spinal cord, because of this fact, then it seems that the deduction is insufficiently proven, for one would not expect to find secondary spinal degeneration from a lesion confined to the temporal and occipital lobes.

Although these observations are extremely suggestive, the number of medullated fibers, which can be demonstrated by the usual myeline stains, are so few that provided they did retain their continuity, their number is not sufficient to account for the functional persistence and absence of degenerative changes in associated areas.

Attention was next directed to the axis-cylinders. A great deal of work has been done upon the intra-cellular fibrils in a variety of normal and pathological conditions, while surprisingly little attention has been paid to the extra-cellular fibrils of the axis-cylinders. The first contributions appeared simultaneously by Bartels (7) and Bielschowsky (8), both of whom studied the condition of the axis-cylinders in multiple sclerosis, using the Cajal and Bielschowsky methods. They found everywhere in the sclerotic areas a surprising number of axis-cylinders of normal direction and appearance. Later, Raubetschek (12) in studying a tuberculoma of the spinal cord by Bielschowsky's method was able to demonstrate the presence of axis-cylinders in the diseased area, but made no report upon the conditions above or below the lesion, nor did he use the Weigert method. All this, naturally, led to some speculation concerning gliomata. Strobe (13) had already shown the presence of medullated fibers in gliomata to be a fairly constant feature; that they increased in number from the center towards the periphery and frequently showed marked degenerative changes. Their number, however, was entirely too small to explain the marked functional persistence, and in order to be consistent, it was commonly held that a great many more fibers could be demonstrated with a reliable axis-cylinder stain.

Bielschowsky (9) had already produced the required stain in 1902, and to him also belongs the credit of having first applied it to the study of gliomata, for in 1904 (10) appeared his first article upon the axis-cylinders in a glioma of the pons. The Weigert preparation showed a number of medullated fibers at the periphery of the tumor, while there were only a few fragments in the center. The author's silver impregnation, however, revealed a great many axis-cylinders in all parts of the tumor. These were considered as persisting fibers and resembled very closely those found in multiple sclerosis.

The following year or so was marked by a lively interest in the extra-cellular fibrils and they were studied in a variety of conditions, such as carcinoma, sarcoma, areas of compression and gliomata; and were found to be present in each case in variable numbers, and in all stages of histologic preservation.

In 1906 appeared another communication by Bielschowsky (11) in which he studied two more gliomata. The first tumor was situated in the left frontal lobe, had advanced upon the corpus striatum, and contained in its posterior portion a few small hemorrhages. Duration—two years. Sections were cut so as to include both center and periphery of the tumor, that is, radially to its center. The technical methods used were hemotoxylin and eosin, Van Gieson, Wiegert, the author's silver impregnation and Benda's glia stain. To the unaided eye the Weigert preparation showed a marked difference between the center and the periphery; the center was golden yellow, while the periphery was dark blue from the presence of numerous medullated fibers. The contrast, however, was not so striking when examined microscopically, and the central portion showed several pale, swollen medullated fibers of irregular contour and many myelin droplets. In the silver impregnation the whole section stained more uniformly and the transition from center to periphery was quite gradual. Microscopically, there were decided histologic changes in the axis-cylinders, considered by the author to be regenerative in character.

In the second case the tumor was situated in the left temporal lobe and extended into the inferior horn of the lateral ventricle. The new growth was quite vascular, contained a small hemorrhage in the center, and numerous fibers from the surrounding brain tissue could be seen radiating towards its center. The microscopic findings were practically the same as in the above case except for the intimate relation of the new fibers to the blood vessels.

In neither case was any report made upon the spinal cord, and the author's attention was more fixed upon the regenerative processes than upon the possibility of anatomical continuity.

Since these studies were published the interesting work by

Herxheimer and Gierlich (14) on neuro-fibrils has made its appearance. The authors have employed Bielschowsky's silver method in normal and pathological conditions with most excellent results. Two gliomata were examined by them, but in both cases the tumor alone was studied. Sections were made from the center and the periphery. The results were practically the same as were found in Bielschowsky's studies except that the axis-cylinders were more nearly normal. It was also observed that in the hemorrhagic and necrotic areas the fibrils were greatly diminished or entirely absent.

While such studies leave no doubt that in these conditions nerve fibers may be found in far greater numbers by a satisfactory axis-cylinder impregnation than by any of the myelin stains, or the usual axis-cylinder stains, it does not appear to be demonstrated that these fibers pass through the new growth without interruption.

Thus it was that my studies were undertaken in order to confirm the result already obtained and to demonstrate, if possible, the continuous course of the persisting fibers.

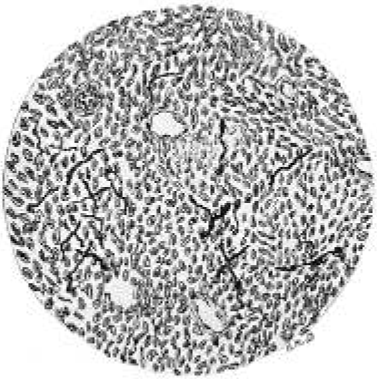
In all, five gliomata were studied. Three are situated in the left cerebral hemisphere, the fourth in the right hemisphere, and the fifth in the pons and medulla. In each case a small piece of tissue was taken from the center of the tumor, and cut by the freezing method into sections varying from ten to fifteen microns each. All sections from each tumor were cut from the same block of tissue. The staining methods used were: hemalum-acid fuchsin, Weigert's and Bielschowsky's silver impregnation for neuro-fibrils.

In the first case the tumor is located in the left occipital and temporal lobes, and measures eight centimeters in its antero-posterior diameter. There are several small hemorrhages scattered throughout and the blood vessels are numerous. The internal capsule is apparently normal. A small piece of tissue was taken from the center of the tumor and from the entire posterior limb of the internal capsule which was divided into anterior, middle and posterior thirds. Sections from each specimen were stained by the three methods employed.

The Tumor.—Hemalum-acid fuchsin showed an extremely vascular tissue made up of cells with round and oval nuclei, and many neuroglia fibers. No nerve fibers are observed in any part of the section.

Weigert Section.—The cellular and vascular characters can still be recognized, and a few swollen, beaded, medullary fragments can be seen (Fig. 1). In the center of the section, where the nerve fibers seem to be least numerous, twenty-seven fragments were counted. Oc. 1. Obj. ⅔. Whereas, if the ⅙ obj. were focused on the same area no medullary fragment could be seen. At the periphery of the section numerous medullary fibers are observed with each magnification.

Bielschowsky Section.—The character of the tissue can still be discerned and many axis-cylinders are seen in all parts of the section (Fig. 2). In that portion of the section which showed the least number of fibers, sixty-eight were counted with the ⅔ obj., and in the same field twenty-four were counted with the ⅙ obj. The axis-cylinders had no definite direction, varied considerably in size, and showed decided evidences of degeneration in certain areas.



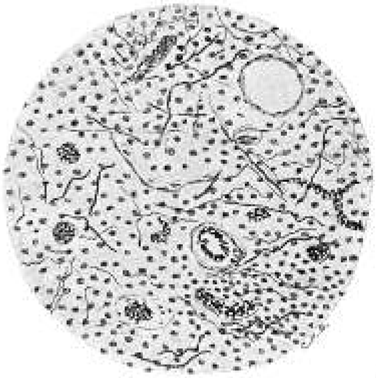


FIG. 1. Weigert preparation from substance of tumor, Case I, showing a few medullated fragments. Oc. 1, Ob. ⅔.

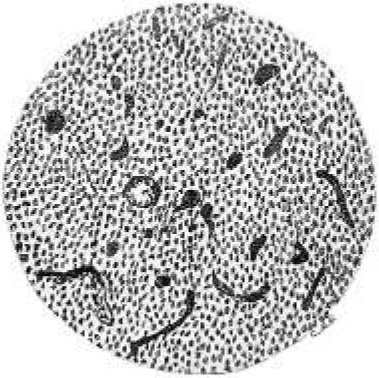
FIG. 2. Bielschowsky preparation from same block of tissue as Fig. 1, showing many axis-cylinders. Oc. 1, Ob. ⅔.

The Internal Capsule.—The anterior third appears to be normal by each of the three stains. The middle and posterior thirds show degenerative changes by all three methods, and a small capillary hemorrhage is observed in the posterior third, and some proliferation of the neuroglia cells. In the degenerated areas a great many more axis-cylinders are observed in the silver preparation than in either of the other two stains. The hemorrhagic area shows a complete absence of medullated fibers in the

Weigert preparation, while the silver preparation shows many fibers in this area.

Although the number of persisting fibers is comparatively small in this case, such has been the usual observation in hemorrhagic gliomata and in areas of secondary softening (14).

In the second case there is a large glioma situated in the left occipital, parietal and temporal lobes, with extension into the left cerebral crus. In its center there is an area of softening. The specimen of tissue taken from the center of the tumor was treated in the manner described and shows in each case such a marked resemblance to the one just reported that one description will serve for both. The second tumor, however, contains a great many more axis-cylinders in the silver preparation than are found in the first case.



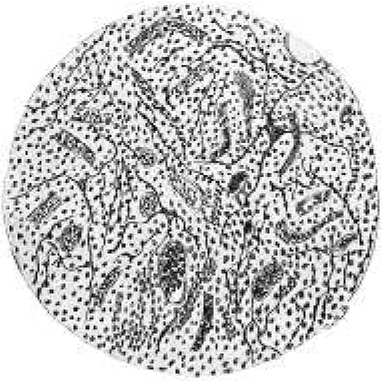


Fig. 3. Weigert preparation from substance of tumor, Case 3, showing an entire absence of fibers. Oc. 1, Ob. ⅔.

Fig. 4. Bielschowsky preparation from same block of tissue as Fig. 3, showing numerous axis-cylinders and two ganglion cells. Oc. 1, Ob. ⅔. No part of this section was free from fibers.

The third tumor involved the right occipital and temporal lobes and is quite hemorrhagic. The internal capsule and thalamus are greatly displaced to the left. The hemalum-acid fuchsin stain is similar to the above two cases. The Weigert preparation shows a complete absence of medullated fibers, while the silver method reveals a great many axis-cylinders (Figs. 3 and 4).

The fourth tumor is extremely large, is gelatinous in places, and is situated in the left cerebral hemisphere. Portions of the occipital and temporal lobes, the internal capsule, thalamus and lenticular nucleus are involved; and there is decided displacement of the surrounding tissue. As in the third tumor there is complete absence of fibers in the Weigert preparation. The silver impregnation shows a number of axis-cylinders, most of which appear quite normal. (This case has been reported by Dr. Charles K. Mills (15), who studied it from the physiological and pathological aspects. His article also includes a gross pathological description of the tumor by Dr. William G. Spiller.)

The fifth case is a tumor of the pons. The basilar portion of the pons is considerably enlarged and presents a lobulated appearance due to the presence of a soft gelatinous growth. The tumor is more pronounced on the left side, where it measures 4.5 c.m. antero-posteriorly, while on the right side it measures only 2.5 c.m. The left middle cerebellar peduncle is involved, and anteriorly the new growth extends into the interpeduncular fossa, where it encroaches upon the left cerebral crus. The new growth in each half of the pons becomes continuous superior to the basilar artery and at the upper border of the pons completely surrounds the artery. On the left side no transverse pontal fibers are observed, while on the right side a few of these fibers may be seen where the middle peduncle enters the cerebellum. Transverse sections through the cerebral hemispheres show decided involvement of the left internal capsule and cerebral crus.

A transverse section through the middle of the pons shows no normal pontal tissue in either half, and the basal and tegmental areas are equally involved. The pyramidal fibers are apparently absent in both sides, having been replaced by extremely gelatinous and translucent tissue. The superficial transverse pontal fibers are entirely absent, while the deep fibers are considerably swollen. The left half of the pons is somewhat larger than the right, and has deflected the aqueduct of Sylvius to the right. There is no evidence of displacement in the basilar portion; but rather a condition of general enlargement. The anterior pyramids appear normal in transverse sections.

The patient was a female and had had symptoms for about one year. The optic discs were greatly swollen; there was slight ataxia; exaggerated reflexes in right arm and leg; no ankle clonus; and Babinski was positive.

A small piece of tissue was taken from the left half of the pons in an area which would normally contain many pyramidal fasciculi. This together with a portion of the two anterior pyamids was sectioned longitudinally and stained as in the preceding cases.

The Tumor.—The hemalum fuchsin stain reveals the gliomatous character. The tissue is not very vascular and there is no positive evidence of nerve fibers.

The Weigert preparation shows a surprising number of medullated fibers normally directed and fairly well preserved (Fig. 5). They do not, however, extend entirely across the section and some of them are swollen and beaded. Areas are also seen in which no medullary substance is present.

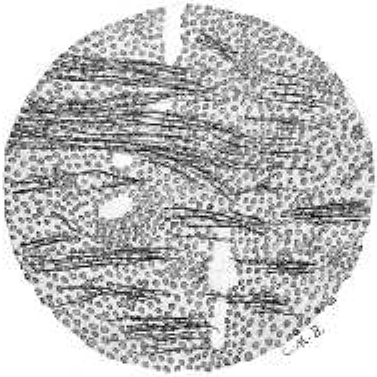


FIG. 5. Weigert stain. Longitudinal section from midst of pontal tumor, showing medullated fibers and areas entirely devoid of fibers. Oc. 1, Ob. ⅔. Case 5.

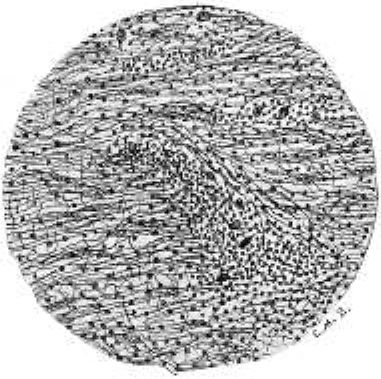
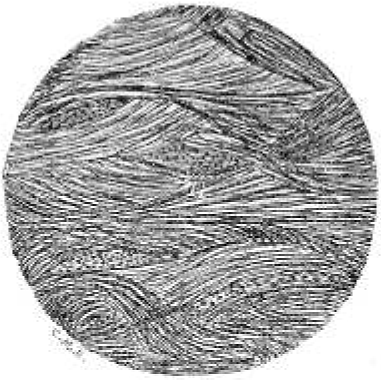


FIG. 6. Bielschowsky preparation, from same block of tissue as Fig. 5, showing countless normal axis-cylinders and a few ganglion cells. This is a fair representation of the entire section. Oc. 1, Ob. ⅔.

The Bielschowsky section shows innumerable axis-cylinders normally directed and surrounded by the infiltrating cells. What astonishes one most is their almost perfect state of preservation (Fig. 6). The fibers are arranged in definite bundles, and numbers of them are seen extending entirely across the microscopic field. There is no evidence of fragmentation, and only occasionally do they show swelling or disintegrative changes. *No part* of the section is free from fibers. Their normal appearance is most interesting since the cases hitherto reported have all shown decided structural changes.

The Pyramids.—The two pyramids are so similar that one description will serve for both. Figs. 7 and 8 represent the left anterior pyramid stained by the Weigert and Bielschowsky methods respectively. In neither case are there definite degenerative changes. The Weigert preparation, in particular, is quite normal looking, the fibers show no swelling or beading, and are present in sufficient numbers. The silver preparation, however, shows some swelling of the axis-cylinders in places. There is no fragmentation and no part of the section is devoid of fibers. A transverse section of the anterior pyramids stained by the Weigert method was studied from a preparation belonging to Dr. Spiller, which he kindly let me use. There was no degeneration in either pyramid.



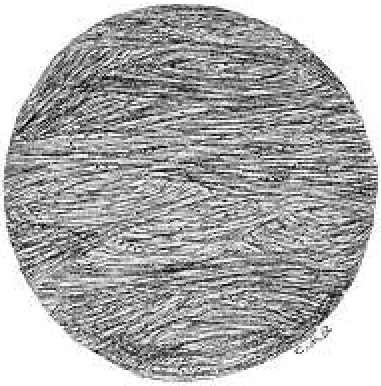


FIG. 7. Weigert preparation from left anterior pyramid cut longitudinally. Case 5. Oc. 1, Ob. ⅔.

FIG. 8. Bielschowsky preparation from same block of tissue as Fig. 7. Oc. 1, Ob. ⅔.

For the sake of completeness and to determine whether there might be some "reaction à distance," sections were made from the right and left paracentral lobules in order to study the Betz cells. They were stained by the Bielschowsky and thionin methods. There was some central chromotolysis in the thionin preparation, though not to a marked degree, and the intracellular fibrils more disintegrating in a few cells. Considering the age of the patient and the increased cerebral pressure with probable circulatory disturbances, such observations are of little value. At any rate, the majority of the cells were perfectly normal.

The first criticism from inquiring minds will naturally be concerning the silver preparations. Are all the fibers found in this case, in particular, really axis-cylinders, or may not some of them be neuroglia fibers, connective tissue, or even artefacts? Bielschowsky does not claim to have furnished an exclusive axis-cylinder stain, and states that in his own hands his method does impregnate neuroglia and connective tissue. The distinction, however, between these different elements is quite easily made, and it is often possible to obtain specimens in which the neuroglia fibers are not at all impregnated, a condition which was obtained in a number of my preparations. In case the neuroglia fibers are apparent, they never stain so intensely as the axis cylinders; are as a rule much smaller; have a more wavy contour; do not arrange themselves in bundles; and are not found running uninterruptedly through the entire section.

Summary and Conclusions

1. In three of my five cases nerve fibers were found in the substance of gliomatous tissue by both Weigert and Bielschowsky methods.

2. Two of the cases showed an entire absence of fibers, or even myelin droplets by the Weigert method, while unmistakable axis-cylinders could be seen in the silver preparation made from the same blocks of tissue. This is due, no doubt, to the greater vulnerability of the myelin sheath and its early disappearance. Thus there is certainly not a very intimate relationship between this sheath and the axis-cylinder, and Brodmann (16) maintains that there is no relation between myelinization and the formation of fibrils. Consequently, in such cases studied by the Weigert method alone, the absence of fibers in the tumor, and the failure to find degenerations in the spinal cord led to the most obvious conclusion that the fibers had been pushed aside.

3. In all five cases a great many more nerve fibers (axis-cylinders) were found by the silver method than in the Weigert preparation.

4. In the fifth case the entire pons was involved, and there was no evidence of the pyramidal fasciculi upon gross examination, yet a section from the tumor substance treated by the Bielschowsky method showed an enormous number of normal axis-cylinders; the anterior pyramids showed no degeneration in either longitudinal or transverse sections; and the Betz cells in the greater part were quite normal. Considering, then, the loca-

tion of this tumor, its long duration, the absence of marked symptoms pointing to upper segment involvement, and the microscopic findings, it seems reasonable to conclude that not only are nerve fibers retained in gliomatous tissue but that a large number persist as uninterrupted axones, passing through the tumor substance.

In conclusion, I wish to express my gratefulness to Dr. William G. Spiller, of the University of Pennsylvania, for placing the material at my disposal and for his many helpful suggestions.

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